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In Silico Testing and in Vivo Experiments with Closed-Loop Control of Blood Glucose in Diabetes

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Abstract: Diabetes technology is currently focused on developing the artificial pancreas - a closed-loop control algorithm linking continuous glucose monitoring (CGM) and subcutaneous insulin delivery. The future development of the artificial pancreas will be greatly accelerated by employing mathematical modeling and computer simulation. Such in silico testing would provide direction for clinical studies, outruling ineffective control scenarios in a cost-effective manner. Thus, computer simulation testing of closed-loop control algorithms is regarded as a prerequisite to clinical trials of artificial pancreas. We therefore present a system for in silico testing of control algorithms consisting of a simulated human metabolic system, simulated CGM and simulated insulin pump. Further, we present an overview of current in vivo clinical trials of CGM and closed-loop control and illustrate the positive effects of CGM by data collected in a clinical trial using the Freestyle Navigator^{TM} (Abbott Diabetes Care, Alameda, CA).

1. INTRODUCTION

Over thirty years ago, the possibility for external regulation of blood glucose (BG) in people with diabetes has been established by studies using intravenous (i.v.) glucose measurement and i.v. infusion of glucose and insulin to maintain normoglycemia by exerting both positive (via glucose or glucagon) and negative (via insulin) control. Systems, such as GCIIS or the better known Biostator, have been introduced and used in hospital setting Pfeiffer et al. (1974), Albisser et al. (1974), Clemens et al. (1977), Marliss et al. (1977), Santiago et al. (1979). These systems were based on variants of the proportional integral derivative (PID) strategy: the injected insulin is proportional to the difference between a fixed target and the measured plasma glucose, as well as to the glucose rate of change. Other types of controllers have also been designed; some based on model-predictive (MPC) strategies counteracting the inherent inertia of exogenous insulin. The major designs can be found in Kraegen et al. (1977), Fischer et al. (1978), Clemens (1979), Broekhuyse et al. (1981), Salzsieder et al. (1985). More work followed, spanning a broader range of control techniques, such as pole placement Salzsieder et al. (1985), adaptive control Fischer et al. (1987), physiologic modeling Sorensen (1985), or linear quadratic Gaussian optimization (LQG) Ollerton (1989), Fischer (1991). However, i.v. closed-loop control remains cumbersome and unsuited for outpatient use. An alternative to extracorporeal i.v. control is presented by implantable i.v.-i.p. systems employing intravenous sampling and intra-peritoneal (i.p.) insulin delivery Leblanc et al. (1986), Selam et al. (1992), Renard (2002). Recently, with the advent of minimally-invasive subcutaneous (s.c.) continuous glucose monitoring (CGM), increasing academic, industrial, and political effort has been focused on the development of s.c.-s.c. systems, generally using CGM coupled with insulin infusion pump and a control algorithm Klonoff (2007). So far, encouraging pilot results have been reported Steil et al. (2006), Weinzimer (2006). A recent United States Senate hearing emphasized the artificial pancreas initiative, see Senate hearing (2006). In September 2006, the Juvenile Diabetes Research Foundation (JDRF) initiated the Artificial Pancreas Project and funded a consortium of university centers to carry closed-loop glucose control research, see The JDRF e-Newsletter (2006).

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2. IN SILICO TESTING OF CLOSED-LOOP CONTROL ALGORITHMS

The future development of the artificial pancreas will be greatly accelerated by employing modeling and computer simulation. Such in silico testing would provide direction for clinical studies, outruling ineffective control scenarios in a cost-effective manner. In the past two decades simulation and computer-aided design have made dramatic progress in all areas of complex engineering systems. In diabetes, prediction of clinical trials has been done by the Archimedes diabetes model Eddy et al. (2003), Eddy et al. (2003b); a company - Entelos, Inc. - specializes in predictive biosimulation. These diabetes simulators, however, are based on population models and as a result, their capabilities are limited to prediction of population averages. For the purposes of artificial pancreas development, a different type of system is needed - one that is capable of simulating the glucose-insulin dynamics of a particular person. We need to emphasize, however, that good in silico performance of a control algorithm does not guarantee in vivo performance. Thus, computer simulation is only a prerequisite to, not a substitute for clinical trials.

The principal components of computer simulation environment recreating in silico a closed-loop control system are presented in Figure 1:

a. A sufficiently large cohort of in silico 'subjects" based on real individual data and spanning the observed variability of key parameters in the general population;

b. Sensor-specific simulator of sensor errors, capable of reproducing the time lag, system and calibration bias, and random noise of s.c. CGM or implantable devices;

c. The model of an insulin pump ensuring discrete insulin delivery and accounting for engineering limitations and the time lag inherent with s.c. insulin injection.

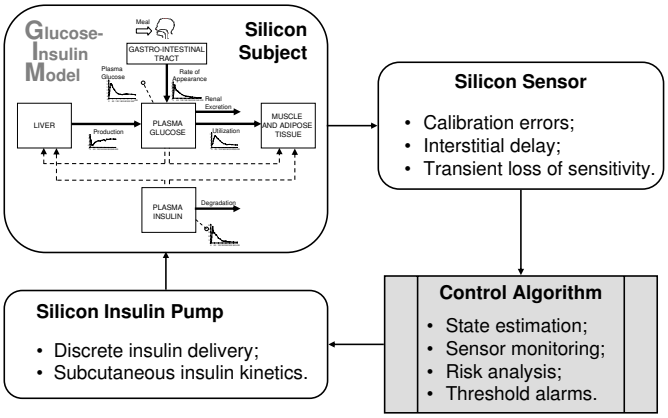

Fig. 1. Principal components of computer simulation environment.

2.1 In silico "subjects"

In silico "subjects" are typically created by fitting a metabolic model to data of individuals collected during clinical trials. Various metabolic models (Dalla Man et al. (2007), Dalla Man et al. (2007b); Hovorka (2005), Sorensen (1985)) have been developed to serve this purpose, with the first two already used for testing of control scenarios. As an example of building an in silico "subject" we present the glucose fluxes (i.e. rate of appearance, endogenous glucose production, etc.) postulated by the Glucose-Insulin Model (Dalla Man et al. (2007):

$$\begin{cases} \dot{G}_p(t) &= EGP(t) + Ra(t) - U_{ii} - E(t) \\ & \quad -k_1 G_p(t) + k_2 G_t(t) \\ \dot{G}_t(t) &= -U_{id}(t) + k_1 G_p(t) - k_2 G_t(t) \\ G(t) &= \frac{G_p(t)}{V_G} \end{cases}$$

with $G_p(0) = G_{pb}$, $G_t(0) = G_{tb}$, $G(0) = G_b$. Here G_p and G_t (mg/kg) are glucose masses in plasma and rapidly-equilibrating tissues, and in slowly-equilibrating tissues, respectively, G (mg/dl) is plasma glucose concentration, suffix b denotes basal state, EGP is endogenous glucose production $(mg/kg/min)$, Ra is glucose rate of appearance in plasma $(mg/kg/min)$, E is renal excretion $(mg/kg/min)$, Uii and Uid are insulin-independent and dependent glucose utilizations, respectively $(mg/kg/min)$, V_G is the distribution volume of glucose (dl/kg), and k_1 and k_2 (min^{-1}) are rate parameters. In addition to glucose fluxes, the detailed model contains equations of insulin kinetics, as well as a compartmental representation of glucose intestinal absorption and the glucose transit through the stomach and intestine. Glucose excretion by the kidney, which occurs if plasma glucose exceeds a certain threshold, is modeled as well Dalla Man et al. (2007). Once the set of equations defining in silico "subjects" is laid out, in silico "population" is created by generating parameter vectors spanning the parameter space of the subject population. As an example of the utility of this approach, a recently developed in silico "population" containing 300 "subjects" in three age groups has been approved by the FDA as a substitute to animal trial in the pre-clinical testing of closed-loop control algorithms.

2.2 In silico sensor

In silico sensor is developed on the basis of a detailed analysis of sensor errors. In general, continuous glucose monitors (CGM) provide detailed time series of consecutive observations upon the underlying process of glucose fluctuations. However, a number of studies have concluded that despite eight years of development, the CGM technology continues to face challenges in terms of sensitivity, stability, calibration, and the physiological time lag between blood and interstitial glucose concentration Gerritsen et al. (1999), Gross et al. (2000), Cheyne et al. (2002), Kovatchev et al. (2004), Clarke et al. (2005), Clarke et al. (2005b), Zisser et al. (2008). While testing sensor accuracy, these studies have typically generated large amounts of sensor-reference glucose data pairs, thereby allowing the decomposition of sensor errors into errors due to calibration, blood-to-interstitial glucose transfer, and random noise King et al. (2007). After generating a random calibration error, the components of sensor error can be modeled as:

(i) Blood-to-interstitium glucose transport described by the equation:

$$\frac{\partial IG}{\partial t} = -\frac{1}{\tau}(IG - BG),$$

where IG is the interstitial and BG is plasma glucose concentration, and τ represents the time lag between the two fluids;

(ii) Noise of the sensor, which is non-white (Gaussian). We therefore use ARMA process for its modeling.

$$\begin{cases} e_1 = v_1 \\ e_n = 0.7(e_{n-1} + v_n) \end{cases}$$

with $v_n \sim \Phi(0,1)$, *i.i.d.*. The sensor noise is ε_n, which is driven by the normally distributed time series e_n. The parameters ξ, λ, δ, and γ are the Johnson system (SU - unbounded system) parameters corresponding to empirical noise distributions established in accuracy trials:

$$\varepsilon_n = \xi + \lambda \sinh\left(\frac{e_n - \gamma}{\delta}\right)$$

2.3 In silico insulin pump

In silico insulin pump is used to model subcutaneous insulin delivery. This has two major specifics that need to be taken into account: (i) time and dynamics of insulin transport from subcutaneous compartment into blood, and (ii) discrete insulin infusion corresponding to stepwise basal pump rate and insulin boluses. Several models of subcutaneous insulin kinetics have been published Nucci et al. (2000), Wilinska et al. (2005). For example, a two compartment model can be assumed to describe insulin kinetics:

$$\begin{cases} \dot{I}_l(t) = -(m_1 + m_3) I_l(t) + m_2 I_p(t) \\ \dot{I}_p(t) = -(m_2 + m_4) I_p(t) + m_1 I_l(t) + Pump(t) \\ I(t) = \frac{I_p(t)}{V_I} \end{cases}$$

with $I_l(0) = I_{lb}$, $I_p(0) = I_{pb}$, $I(0) = I_b$ where Ip and Il $(pmol/kg)$ are insulin masses in plasma and in liver, respectively, I $(pmol/l)$ plasma insulin concentration, suffix b denotes basal state, Pump is the external subcutaneous insulin pump; m_1, m_2, m_3, m_4 (min^{-1}) are rate parameters. If implantable insulin pump is to be simulated, different models reflecting the kinetics of i.v. insulin would need to be used.

Exemplifying the "in silico" testing of a pre-meal insulin bolus, Figure 2 presents the glycemic reaction of three "silicon subjects" after a meal containing 75 grams of carbohydrate, while Figure 3 presents the reaction of one "subject" to three meals with different carbohydrate content: 75, 85, and 95 grams.

3. IN VIVO TRIALS OF CONTINUOUS GLUCOSE MONITORING AND CLOSED-LOOP CONTROL

CONTINUOUS GLUCOSE MONITORING

The feedback of detailed continuous monitoring information to patients with diabetes has been shown to have positive influence on their glycemic control, including reduction in glucose variability, time spent in nocturnal hypoglycemia, time spent in hyperglycemia, and lower glycosylated hemoglobin Klonoff (2005), Garg et al. (2006), Deiss et al. (2006), Kovatchev et al. (2007). As reported

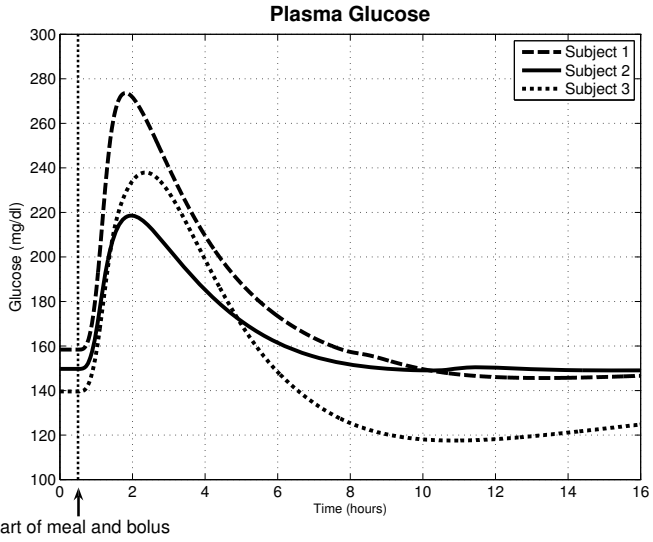

Fig. 2. Glycemic reaction of three "silicon subjects" after a meal containing 75 grams of carbohydrate.

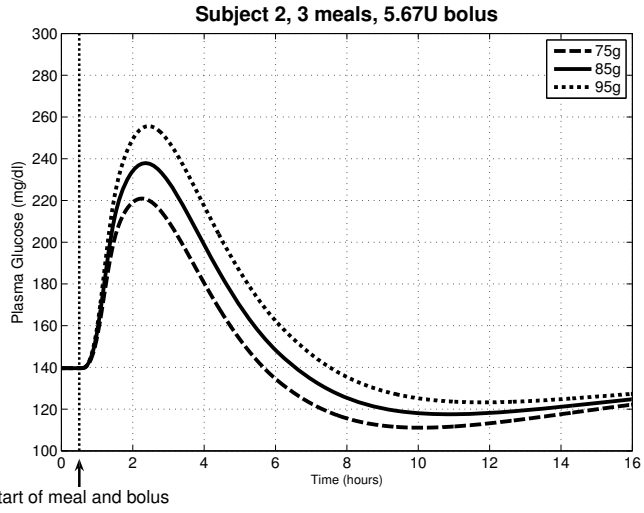

Fig. 3. Glycemic reaction of one "subject" to three meals with different carbohydrate content.

recently, the first effects occurring within days of initiation of CGM were marked reductions in glucose variability and associated risks, not accompanied by reduction in average glycemia Kovatchev et al. (2007b). The proposed here criteria have been shown to be quite sensitive to these effects Kovatchev et al. (2005),McCall et al. (2006). Thus, in addition to traditional characteristics such as average BG and time within target range, we suggest computing in one-hour increments: (i) the Low Blood Glucose Index (LBGI), which captures the risk of the control algorithm triggering hypoglycemia; (ii) the High Blood glucose index (HBGI), which captures the propensity of the algorithm to stay above the target range, and (iii) the absolute rate of glucose change, which captures the smoothness of the algorithm. To illustrate these measures, Figure 4 presents the effect of CGM in a group of 123 patients who were kept blinded to the readings of the device (Freestyle Navigator^{TM}) for 20 days and then unblended, exercising

behavioral open-loop control based on CGM. Panel A shows that average glucose did not change as a result of un-blinding the CGM at day 20, while Panel B shows dramatic risk-reduction effect for hypoglycemia (LBGI) and hyperglycemia (HBGI).

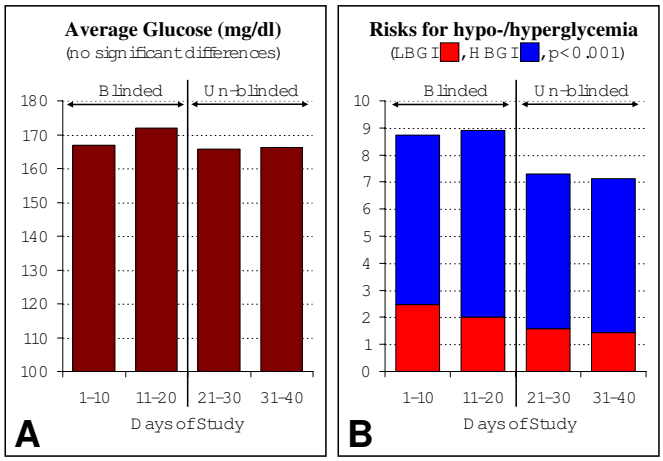

Fig. 4. Effect of CGM in a group of 123 patients.

4. CLOSED-LOOP CONTROL

As indicated in the introduction, closed-loop control is still in infancy. As reported by Renard Renard (2002), closed-loop control based on implantable devices showed promising results. The European Advanced insulin infusion using a control loop (Adicol) project Hovorka et al. (2004) proposed a modular concept of extracorporeal s.c.-s.c. closed-loop composed of a minimally invasive subcutaneous glucose system, a PocketPC running MPC algorithm, and an insulin pump. Throughout the project, however, i.v. glucose monitoring has been used due to the lack of a functional real-time CGM, delayed by 30 min to mimic s.c. monitoring. It was therefore concluded that the CGM is the limiting factor in the development of a viable s.c.-s.c. system Hovorka (2005). Recently, several real-time s.c. CGM have been introduced: Guardian^{RT} (Medtronic, Northridge, CA), DexCom^{TM} STS^{TM} (DexCom, Inc. San Diego, CA), and Freestyle Navigator^{TM} (Abbott Diabetes Care, Alameda, CA). The next logical step was taken by the MiniMed Paradigm® REAL-Time Insulin Pump and Continuous Glucose Monitoring System approved by the U.S. Food and Drug Administration in April 2006 as the first open-loop control system available to people with diabetes. Closed-loop control versions of this system have been tested as well: Steil et al reported 30-hour trial in 10 patients with T1DM, which proved conceptually the possibility of fully-automated external closed-loop insulin delivery Steil et al. (2006). In November 2006, Weinzimer reported data from the testing of the ePID System in 17 adolescents with T1DM: $N = 8$ in automated closed-loop mode and $N = 9$ in closed-loop combined with pre-meal insulin bolus ($N = 9$) Weinzimer (2006). In this 24-hour test average glucose of 144 ± 52 mg/dl was achieved, with three nocturnal episodes of hypoglycemia and a no hypoglycemia during the day; the pre-meal bolus resulted in approximately 30 mg/dl attenuation of postprandial glucose excursions. Finally, in animal experiments, dual insulin+glucagon model-predictive closed-loop control has been tested successfully El-Khatib et al. (2007).

5. CONCLUSIONS

Continuous glucose monitoring has already proven its utility in optimizing the glycemic control of people with diabetes. The first short-term effect of CGM appears to be a reduction of glucose variability. This is because the traditional measures of average glycemia, such as HbA1c, change slowly over time and are insensitive to short-term treatment interventions. Based on CGM and insulin delivery, pilot clinical trials of closed-loop control are under way. Comprehensive computer simulation has the potential to greatly accelerate their progress. Its principal components should include: (i) a mathematical model of the human metabolic system; (ii) a generator of CGM errors, and (iii) a representation of discrete insulin delivery and subcutaneous insulin transport. A final essential component of both in silico and in vivo trials is a set of outcome measures capable of capturing the variability-reducing effects of the relatively short-term (2-3 days) trials of CGM use or closed-loop control.

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